Dermatologic and Ophthalmic Drugs Advisory Committee Meeting

Afternoon Session

FDA Introductory Remarks

Kendall A. Marcus, MD
Director
Division of Dermatology and Dental Products

March 9, 2015

Pediatric Product Development for Dermatologic Indications

- ***Historical Perspectives***
  - Products for psoriasis
  - Pegylated interferon/ribavirin for hepatitis C
  - Lipromatase for pancreatic insufficiency due to cystic fibrosis
- ***Questions for consideration***
  - Systemic therapies for refractory atopic dermatitis

Historical Perspective - Psoriasis Approved Products for Adults

Biologics

- Etanercept (TNF blocker)
- Adalimumab (TNF blocker)
- Infliximab (TNF blocker)
- Ustekinumab (IL-12/IL-23 antagonist)
- Secukinumab (IL-17A antagonist)

Drugs

- Acitretin
- Methotrexate
- Cyclosporine
- Apremilast

Historical Perspective
Biologic Products for Psoriasis

- ***Etanercept*** (2008)
  - Pediatric study conducted and data submitted to FDA in a marketing application
  - Taken to public advisory committee for malignancy concerns
    - Conclusion: Evidence neither confirms nor refutes
  - Application subsequently withdrawn
  - Sponsor released from pediatric study requirements

Historical Perspective Products for Psoriasis

Pediatric study requirements following etanercept experience

- ***Adalimumab*** Released
- ***Infliximab*** Waived
- ***Ustekinumab*** Deferred
- ***Secukinumab*** Waived <6 yrs
  Deferred ≥ 6 yrs
- ***Methotrexate*** Waived
- ***Apremilast*** Waived <6 yrs
  Deferred ≥ 6 yrs

Historical Perspective Interferon/Ribavirin

- Until recently interferon/ribavirin was the standard of care for hepatitis C
- Serious adverse events associated with use include
  - Neuropsychiatric effects
  - Depression/suicidality
  - Bone marrow suppression
  - Infections
  - Eye disorders
  - Autoimmune and endocrine disorders
  - Cardiovascular disorders
  - Colitis and pancreatitis

Historical Perspective Interferon/Ribavirin

- Pediatric study enrolled 114 subjects
  - At 48 weeks of treatment
    - Delay in weight and height increases observed
  - At two year post-treatment follow-up
    - 16% of subjects remained 15 percentiles or more below baseline weight curve
    - 11% remained 15 percentiles or more below their baseline height curve.

Historical Perspective
Lipromatase for Pancreatic Insufficiency

- Pediatric study enrolled 214 subjects w/ cystic fibrosis
  - Mean height, weight and BMI z-scores appeared to decline for first 2-3 months and then stabilize
  - Observed in both 7-11 yr and 12-16 yr age groups
  - Long-term outcomes unknown

Questions to Consider
Systemic Therapies for Refractory AD

- Is there an unmet medical need for pediatric populations?
- How much data should be collected in adults prior to pediatric evaluation?
- How much uncertainty is tolerable when considering the timing of initiation of pediatric studies?
- Does the potential for novel safety issues in pediatric populations change the risk/benefit?
- Do we need to know if a drug has long term adverse effects in pediatric population?
- Describe the appropriate pediatric population.

Atopic Dermatitis Inadequately Responsive to Topical Therapy-- Overview and Available Therapy

Jill Lindstrom, MD, FAAD
Lead Medical Officer
Division of Dermatology and Dental Products
Food and Drug Administration

Outline

- Atopic dermatitis (AD)
  - Clinical presentation
  - Quality of life
  - Comorbidities
- Treatment of AD
  - General approach—AAD Guidelines
  - Available therapies for atopic dermatitis inadequately responsive to topical therapy
  - Dupilumab: example of a product in development—Jane Liedtka, MD

Atopic Dermatitis

- Chronic inflammatory pruritic skin disease
- Prevalence
  - 15-30% children
  - 2-10% adults
- Onset in childhood
  - 45% by 6 months
  - 60% by 1 year
  - 85% by 5 years
- 1/3 persist into adulthood
- ~18% severe disease (Hanifin 2007)

Clinical Presentation

- Pruritus
- Cutaneous manifestations
  - Erythematous papules, vesicles, plaques, erosions
    - Scale, crust
    - Lichenification
    - Hypopigmentation
  - Distribution
    - Face, neck, extensor surfaces
    - Flexures
    - Spares groin
  - Xerosis

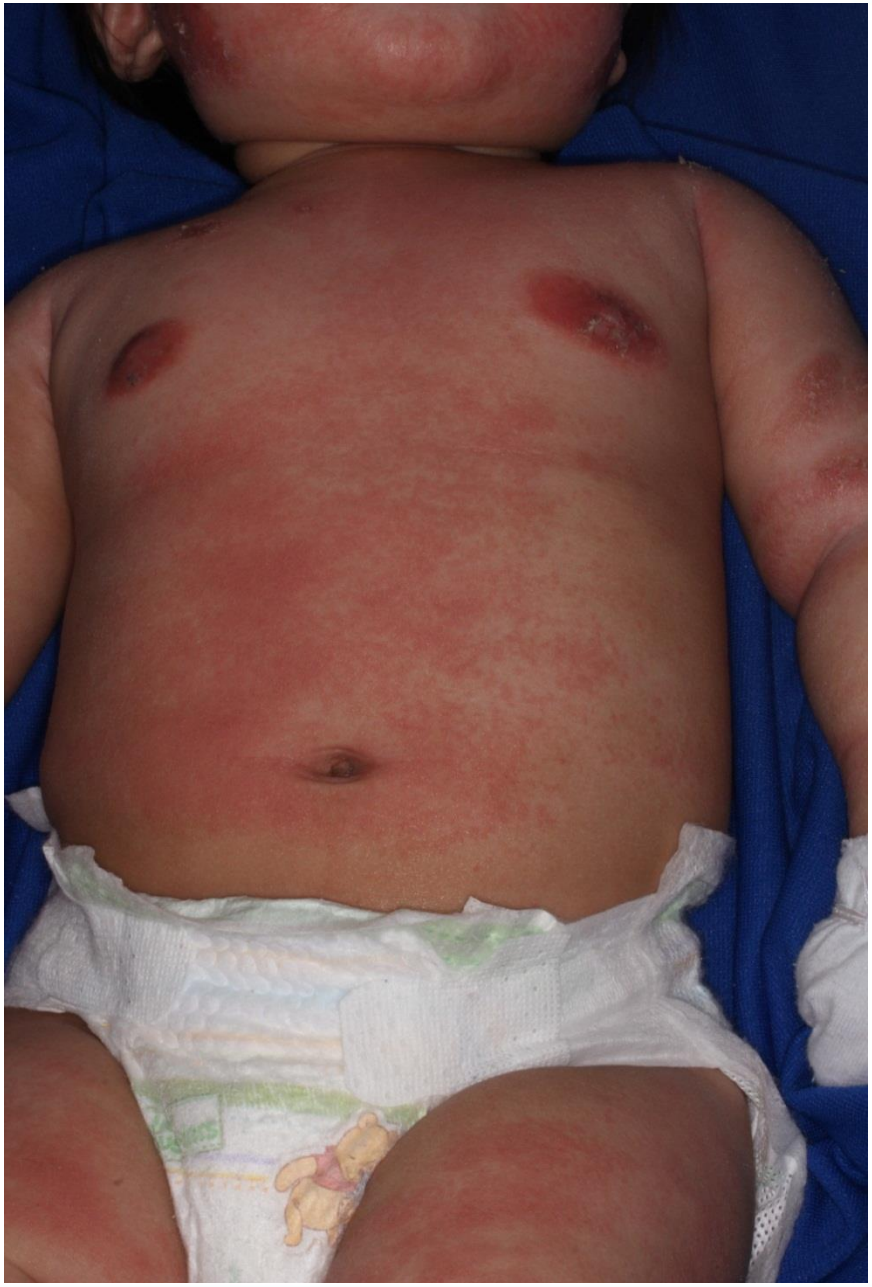


Image courtesy of Amy Paller, MD

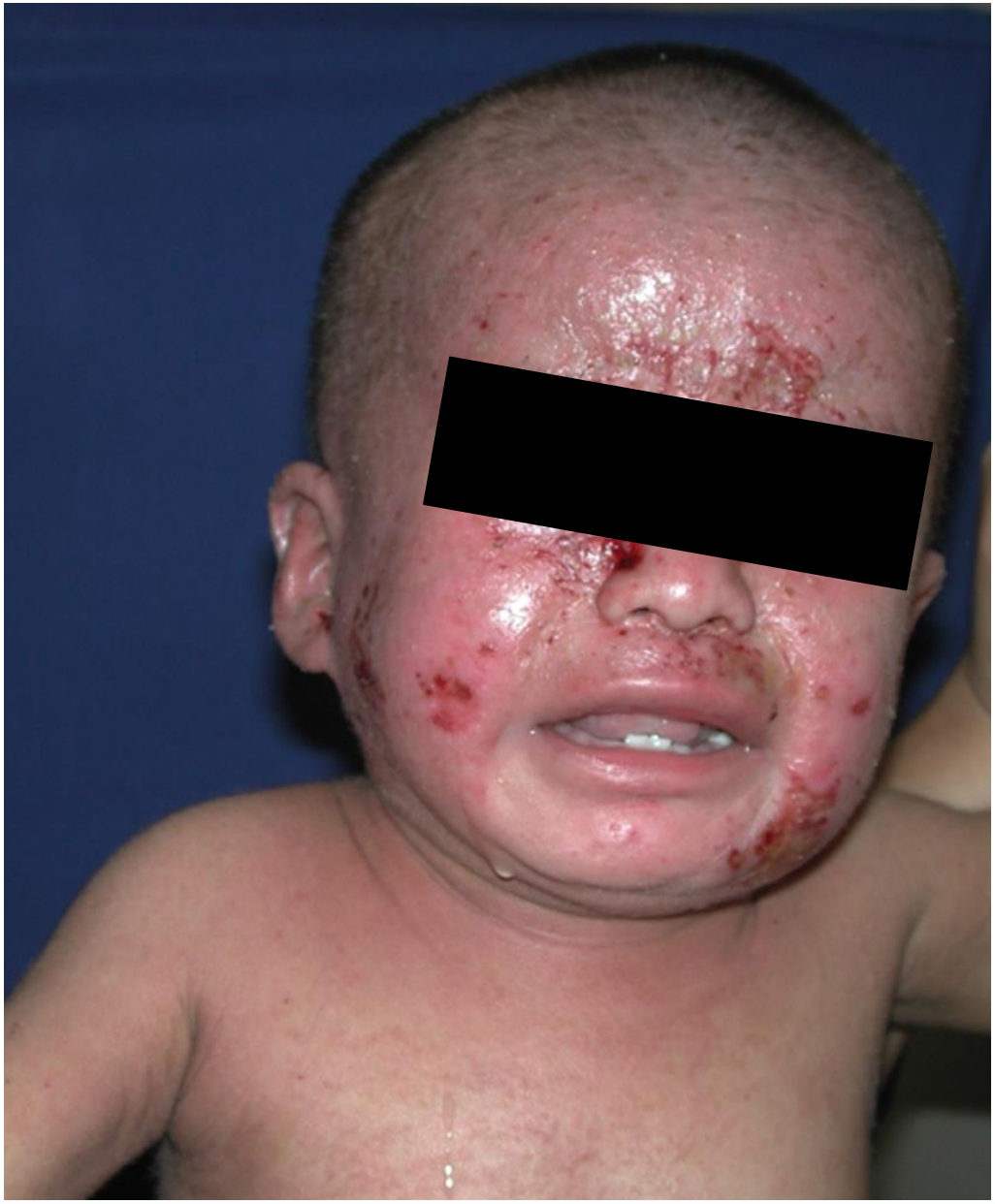
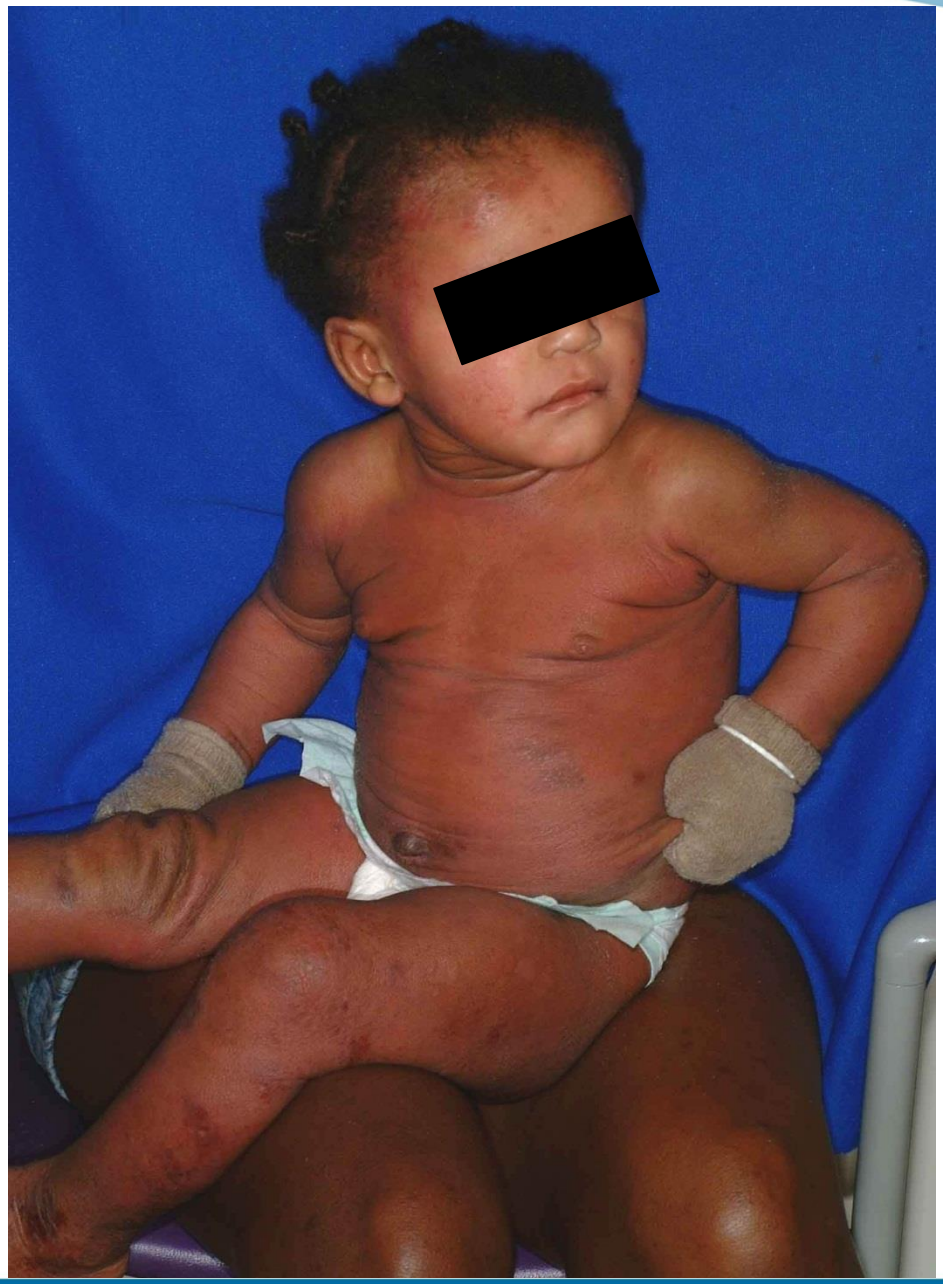


Image courtesy of Larry Eichenfield, MD



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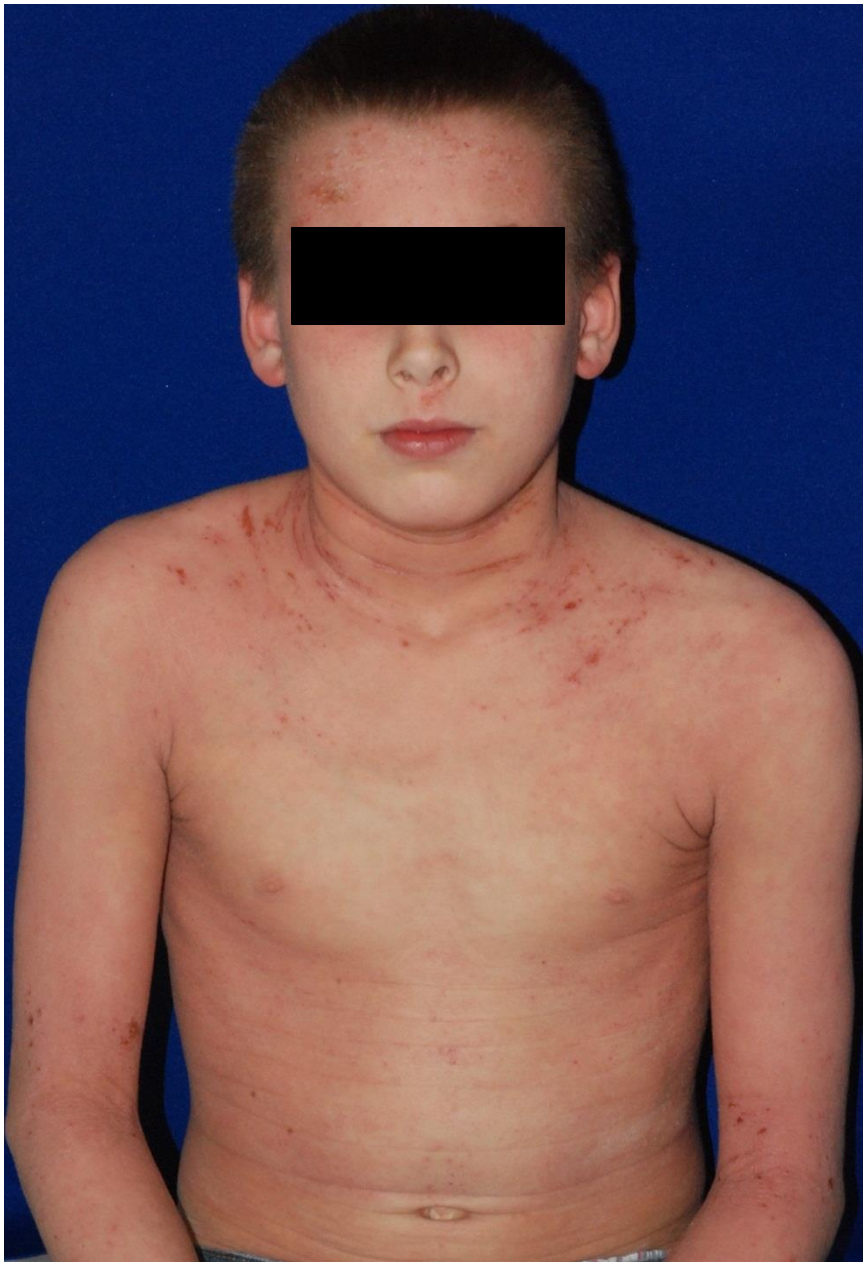

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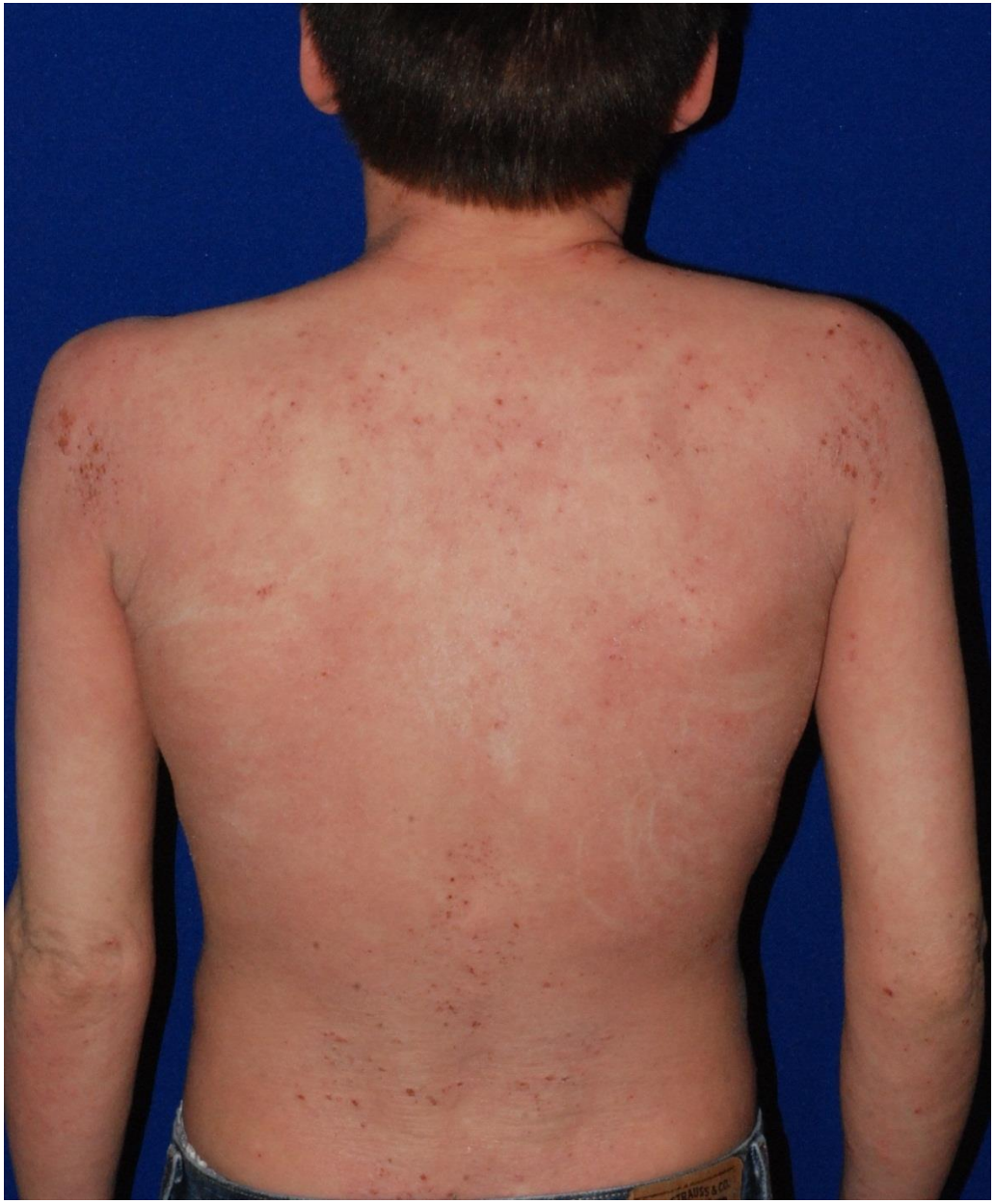

Image courtesy of Amy Paller, MD

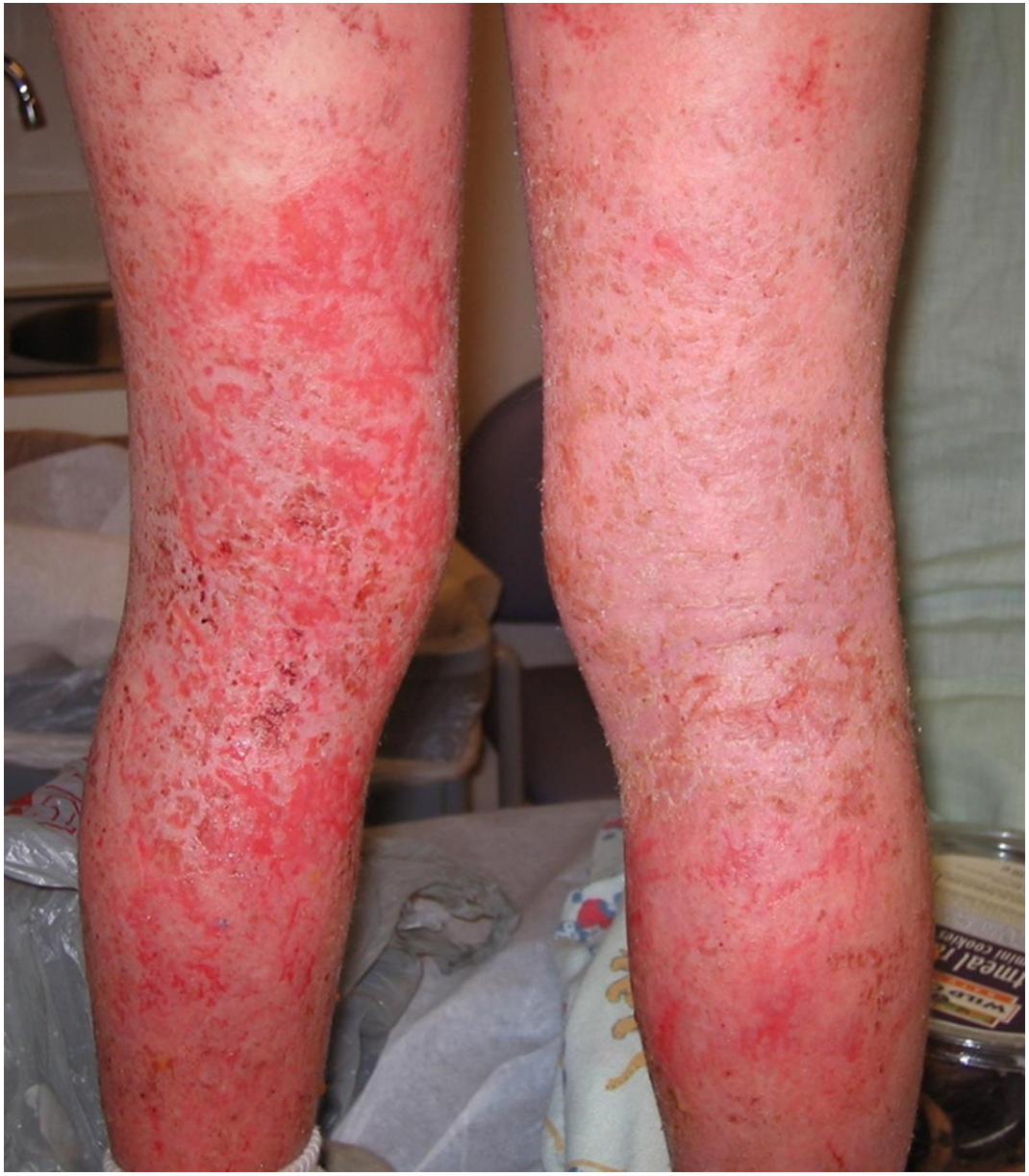

Image courtesy of Larry Eichenfield, MD

Children's Quality of Life Impaired

- Health-related quality of life (HRQL) is impaired in children with atopic dermatitis
- Impairment correlates with disease severity
- HRQL impairment in generalized AD
  - exceeds that in asthma, epilepsy, and diabetes
  - comparable to that in renal disease or cystic fibrosis
  - equals (child) or exceeds (parent) that in psoriasis

Beattie P, Lewis-Jones M; BJD 2006

Family Quality of Life Impaired

- Impairment correlates with disease severity
- Scores comparable to (mild AD) or exceed (moderate or severe AD) those of families of children with diabetes
- Daily time used for treatment: 1.5 hours (mild) to 3 hours (mod, severe)
- Daily hours sleep lost by children: 1 hour (mild) to 2 hours (mod, severe)
- Hours sleep lost by parents: 1 to 2 hours

Ben-Gashir M; Curr Opin Allergy Clin Immunol 2003
Su J, et. al. Arch Dis Child 1997

Family Impact of Childhood Atopic Dermatitis

- 74% burden of care related to practical considerations
- 71% feelings of guilt, exhaustion, frustration, resentment and helplessness
- 61% family life was not normal: e.g., no pet, diet affected, restriction of use of household products
- 63% sleep impairment in children and siblings
- 60% school difficulties: teasing, bullying in school
- 54% behavioral disturbances during disease flares
- 29% personal relationships impaired

Lawson, et. al. BJD 1998.

Sleep Disruption

- Affects up to 60% of children with atopic dermatitis
  - Up to 85% during disease flares
- Sleep latency, increased nocturnal wakefulness, longer latency to REM
- Correlated with severity of atopic dermatitis
- Behavioral deficits, decreased neurocognitive function

Kafferman G, et al. 2014. Sleep Medicine Reviews; 14:359-369.

Psychiatric Comorbidities—Children with AD

- ADD/ADHD
- Depression
- Anxiety
- Conduct disorder
- Autism,
- Learning delay
- Injury requiring medical attention

Garg N, Silverberg J. Ann Allergy Asthma Immunol. 2014; 112:525-532.

Allergic Disease

- Increased prevalence and severity of asthma
  - AD: ~25% asthma
  - Severe AD: ~36% asthma, 36% severe asthma
- Increased prevalence and severity of rhinitis
  - AD: ~34% rhinitis
  - Severe AD: ~40% rhinitis, ~30% severe rhinitis
- Food allergies
  - AD: ~15% food allergies, ~26% severe food allergies
  - Severe AD: ~27% food allergies, ~48% severe food allergies

Silverberg J, Simpson E. Ped Allergy and Immunol 2013; 24:476-486

Infections

- Cutaneous infections
  - Bacterial infections: *Staphylococcus aureus*
  - Viral infections
    - HSV, molluscum contagiosum, HPV
    - eczema herpeticum, eczema coxsackium, eczema vaccinatum
- Extracutaneous infections
  - Recurrent ear infections
  - Strep throat
  - Influenza/pneumonia
  - Sinus infections
  - Urinary tract infections

Silverberg J, Silverberg, N. J Allergy Clin Immunol 2013; 133(4): 1041-7.

Central Obesity and High Blood Pressure

- Case-control study in US of 132 children with moderate to severe AD and 143 healthy controls
- Moderate to severe AD associated with
  - BMI in 97th percentile
  - Waist circumference $\geq$85th percentile (central obesity)
  - Higher systolic and diastolic blood pressure
    - Controlled for age, sex, race/ethnicity, BMI, WC, prior prednisone or cyclosporine use

Silverberg J, et al. Central Obesity and High Blood Pressure in Pediatric Patients with Atopic Dermatitis. JAMA Dermatol. 2015;151(2:144-152).

Outline

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  - Quality of life
  - Comorbidities
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  - Available therapies for atopic dermatitis inadequately responsive to topical therapy
  - Dupilumab: example of a product in development—Jane Liedtka, MD, FAAD

Treatment of Atopic Dermatitis

- Nonpharmacologic measures
  - Moisturizers
  - Bathing practices, bleach baths
  - Wet-wrap therapy
- Topical corticosteroids
  - Multiple products approved for treatment of AD
  - Labeling may contain age restrictions
- Topical calcineurin inhibitors-second line
  - Tacrolimus ointment: moderate to severe atopic dermatitis
  - Pimecrolimus cream: mild to moderate atopic dermatitis

Eichenfield L, et. al. Guidelines of care for the management of atopic dermatitis Section 2. Management and treatment of atopic dermatitis with topical therapies. J Am Acad Dermatol 2014; 71(1): 116-132.

Systemic Therapy—AAD Guideline Recommendations

- "…recommended for the subset of adult and pediatric patients in whom optimized topical regimens using emollients, topical anti-inflammatory therapies, adjunctive methods, and/or phototherapy do not adequately control the signs and symptoms of the disease…"
- "…systemic immunomodulating agents may also be used in patients whose medical, physical, and/or psychological states are greatly affected by their skin disease, which may include negative impact on work, school performance, or interpersonal relationships."

Sidbury R, et al. Guidelines of care for the management of atopic dermatitis Section 3. Management and treatment with phototherapy and systemic agents. J Am Acad Dermatol 2014; 71(2): 327-349.

Available Therapies

- Labeling, AAD Guidelines

Drug	Approved indication	AAD Guidelines
Systemic corticosteroids	✓	✓
Cyclosporine		✓
Azathioprine		✓
Methotrexate		✓
Mycophenolate mofetil		✓

Sidbury R, et al. Guidelines of care for the management of atopic dermatitis Section 3. Management and treatment with phototherapy and systemic agents. J Am Acad Dermatol 2014; 71(2): 327-349.

Systemic Corticosteroids

- Betamethasone acetate and betamethasone sodium phosphate
- Cortisone acetate
- Dexamethasone and dexamethasone sodium phosphate
- Hydrocortisone, hydrocortisone sodium succinate and cypionate
- Methylprednisolone, methylprednisolone sodium succinate and acetate
- Prenisolone, prednisolone acetate and prednisolone sodium phosphate
- Prednisone
- Triamcinolone acetonide

Systemic Corticosteroids-Labeling

- Indication: control of severe or incapacitating [atopic dermatitis] intractable to adequate trials of conventional treatment
- No clinical trial data for atopic dermatitis
- Incomplete or absent information about pediatric dosing
- Live vaccines contraindicated; vaccine responses may be impaired
- Warnings:
  - Growth impairment, osteoporosis
  - Hypothalamic-pituitary-adrenal (HPA) axis suppression
  - Increased risk of infections
  - Psychiatric manifestations: insomnia, depression, psychosis
  - Posterior subcapsular cataracts, glaucoma

Systemic Corticosteroids

- AAD Guidelines:

  "…systemic steroids (oral or parenteral) should generally be avoided in adults and children with AD because the potential short- and long-term adverse effects…largely outweigh the benefits."

  "Systemic steroids may be considered for short-term use in individual cases [in which] other systemic or phototherapy regimens are being initiated and/or optimized."

Cyclosporine

- AAD Guidelines: reduction in signs and symptoms of atopic dermatitis in both pediatric and adult patients
- Not approved in the US for treatment of atopic dermatitis
- Labeling:
  - Limited pediatric dose information
  - Decreased efficacy of vaccines; avoid live vaccines
  - Boxed Warning
    - Malignancies
    - Infections
    - Hypertension
    - Nephrotoxicity, structural renal damage

Azathioprine

- AAD Guidelines: 26-37% of subjects with AD improved
- Not approved for treatment of atopic dermatitis
- Labeling:
  - No pediatric-specific dose information
  - Boxed Warning: Malignancies, including lymphoma, hepatosplenic T-cell lymphoma, and skin
  - Warnings
    - Leukopenia, thrombocytopenia, anemia, pancytopenia
    - Serious infections
    - Nausea, vomiting, gastrointestinal hypersensitivity reaction
    - Mutagen, teratogen

Methotrexate

- AAD Guidelines: treatment effect unclear
- Not approved for treatment of atopic dermatitis
- Labeling:
  - Limited pediatric-specific dose information
  - Decreased efficacy of vaccines; avoid use of live vaccines
  - Boxed Warning
    - Hepatotoxicity, fibrosis, cirrhosis
    - Lymphoma
    - Anemia, pancytopenia, leukopenia, neutropenia, thrombocytopenia
    - Interstitial pneumonitis
    - Diarrhea, ulcerative stomatitis, hemorrhagic enteritis, perforation
    - Toxic epidermal necrolysis, Stevens-Johnson syndrome
    - Nephrotoxicity, acute renal failure
    - Fetal death and congenital anomalies

Mycophenolate mofetil

- AAD Guidelines: alternative therapy; treatment effect variable
- Not approved for treatment of atopic dermatitis
- Labeling:
  - Limited pediatric-specific dose information
  - Decreased efficacy of vaccines; avoid use of live vaccines
  - Boxed Warning
    - Malignancy, lymphoma
    - Serious infection
    - Pregnancy loss and congenital malformations
  - Warnings
    - Anemia, pancytopenia, leukopenia, neutropenia, thrombocytopenia
    - Diarrhea and ulcerative stomatitis
    - Toxic epidermal necrolysis, Stevens-Johnson syndrome

Summary

- AD can be a serious disease, with multiple comorbidities and significant impact on patients' and families' quality of life
- Published practice guidelines recommend use of systemic treatment for patients in whom optimized topical therapy is unsuccessful or whose disease significantly impacts their life
- Available therapies include systemic corticosteroids and systemic immunosuppressant drugs (off-label)

Dupilumab as an Example of a Product in Development for Atopic Dermatitis Inadequately Responsive to Topical Therapy

Jane Liedtka, MD, FAAD
Medical Officer
Division of Dermatology and Dental Products
Food and Drug Administration

Dupilumab

- Fully human monoclonal antibody
- Blocks IL-4 and IL-13
- IL-4 and IL-13 are key drivers of type 2 helper T-cell (Th2)–mediated inflammation
- Atopic Dermatitis (AD) has been classified as a Th2-dominated disease
- Studied in adults with asthma and AD

[1]Beck LA, Thaçi D, Hamilton JD, et al. Dupilumab treatment in adults with moderate-to-severe atopic dermatitis. N Engl J Med. 2014;371:130-9

Dupilumab

- Beck et al. reported studies on dupilumab treatment in adults with moderate-to-severe AD in 2014.[1]
- 4 randomized, double-blind, placebo-controlled trials of once weekly dupilumab in moderate to severe AD not responsive to topical therapy

[1]Beck LA, Thaçi D, Hamilton JD, et al. Dupilumab treatment in adults with moderate-to-severe atopic dermatitis. N Engl J Med. 2014;371:130-9

Dupilumab-Inclusion Criteria

- 18 years and older
- Investigator's Global Assessment scale (IGA) ≥ 3 (moderate) on a 5 grade scale
- Eczema Area and Severity Index (EASI) ≥ 12-16
- Body Surface Area (BSA) ≥ 10-15%
- A diagnosis of AD for at least 2-3 years

[1]Beck LA, Thaçi D, Hamilton JD, et al. Dupilumab treatment in adults with moderate-to-severe atopic dermatitis. N Engl J Med. 2014;371:130-9

Dupilumab Trials

Study	Phase	Type	Duration	# of Subjects	Location
M4A	1	Sequential -dose escalation monotherapy	4 weeks	Placebo=6 Dupilumab75 mg =8 Dupilumab150 mg =8 Dupilumab300 mg =8	US
M4B	1	Sequential -dose escalation monotherapy	4 weeks	Placebo=10 Dupilumab150 mg =14 Dupilumab300 mg =13	Multinational
C4	2	Combination Rx with TCS*	4 weeks	Placebo + TCS=10 Dupilumab300mg + TCS=21	Europe
M12	2	Monotherapy	12 weeks	Placebo = 54 Dupilumab 300 mg =55	Europe

*TCS=topical corticosteroids

[1]Beck LA, Thaçi D, Hamilton JD, et al. Dupilumab treatment in adults with moderate-to-severe atopic dermatitis. N Engl J Med. 2014;371:130-9

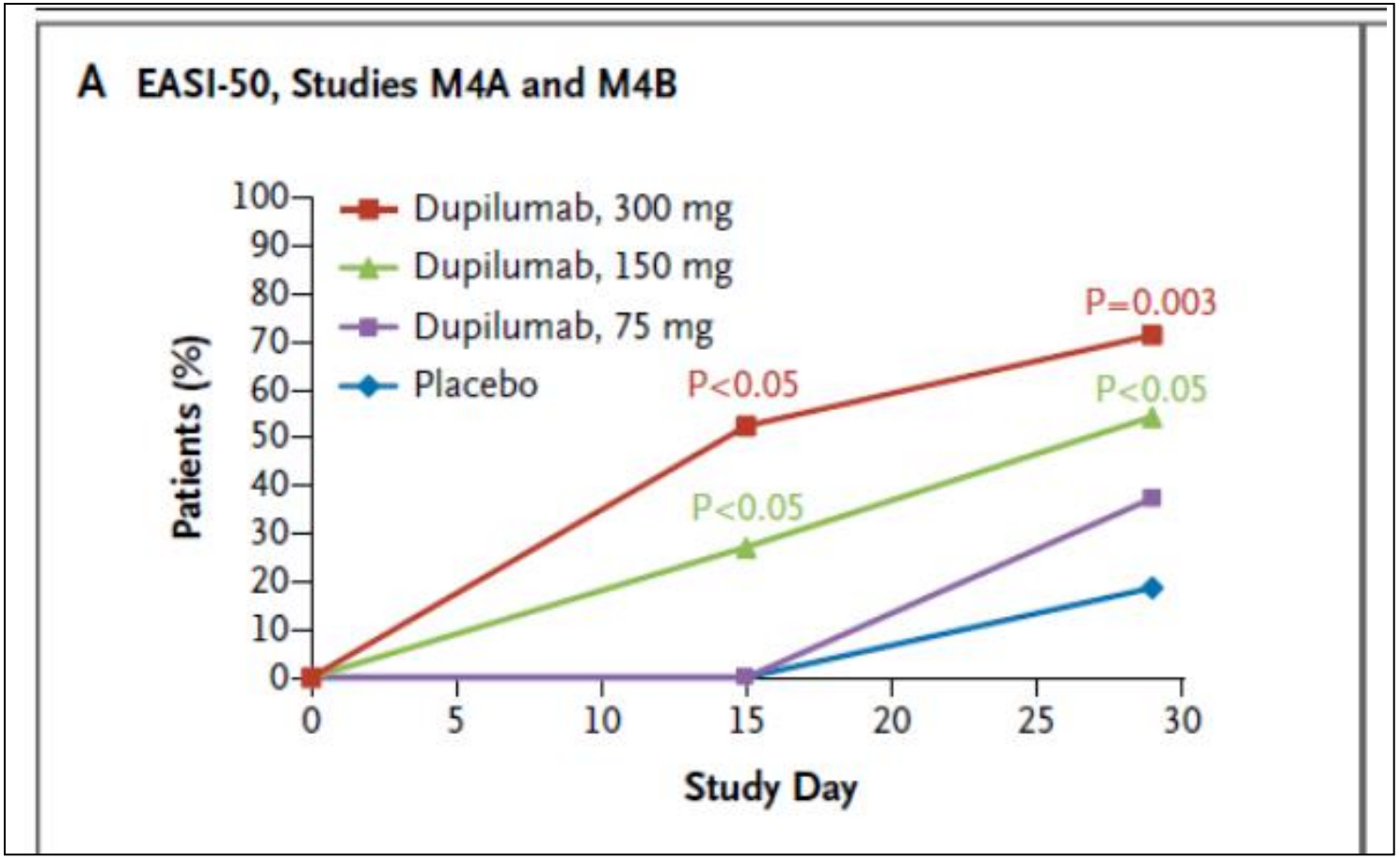
Clinical Characteristics at Baseline

Characteristic	4 wk monotherapy		12 week monotherapy		4 wk Combination with TCS	
	Placebo N=16	Dupilumab N=51	Placebo N=54	Dupilumab N=55	Placebo N=10	Dupilumab N=21
EASI score[2]	23	30	31	28	24	23
IGA score[3]	3.6	3.8	4.0	3.9	3.4	3.4
BSA (%)[4]	40	51	51	47	39	40
Pruritus NRS[5]	5.8	6.0	5.8	6.1	5.0	6.4

[2] rounded to the nearest digit [3]rounded to the nearest digit [4]rounded to the nearest tenth [5]numerical rating score (0-10), rounded to the nearest tenth

[1]Beck LA, Thaçi D, Hamilton JD, et al. Dupilumab treatment in adults with moderate-to-severe atopic dermatitis. N Engl J Med. 2014;371:130-9

Results-Key Efficacy Endpoints (M4A + M4B combined)



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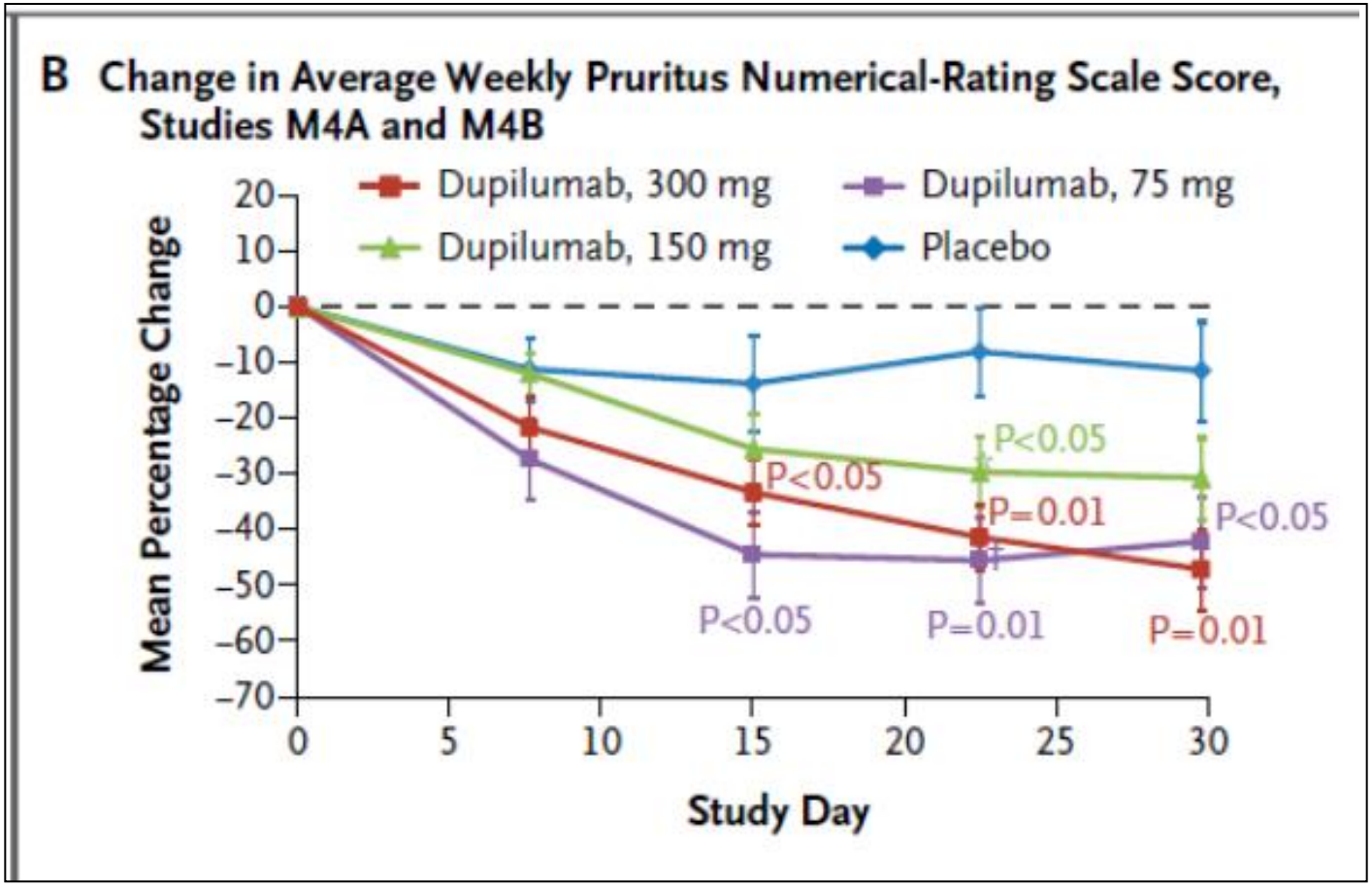


[1]Beck LA, Thaçi D, Hamilton JD, et al. Dupilumab treatment in adults with moderate-to-severe atopic dermatitis. N Engl J Med. 2014;371:130-9

Results-Key Efficacy Endpoints In Combination With Topical Corticosteroids (TCS)

- EASI 50 response

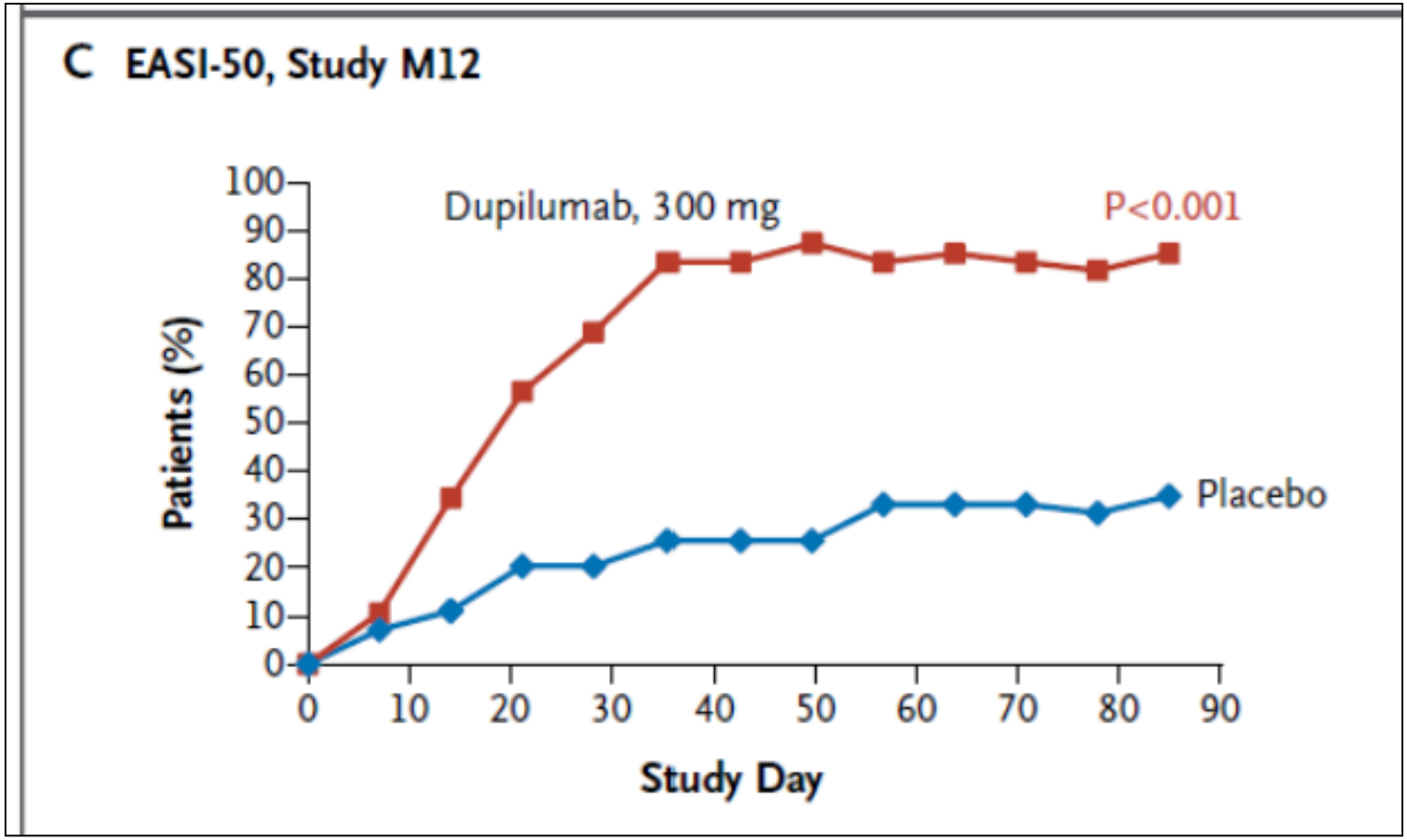
  Dupilumab 100%

  Placebo 50%

- Dupilumab-treated subjects decreased TCS use by 50%

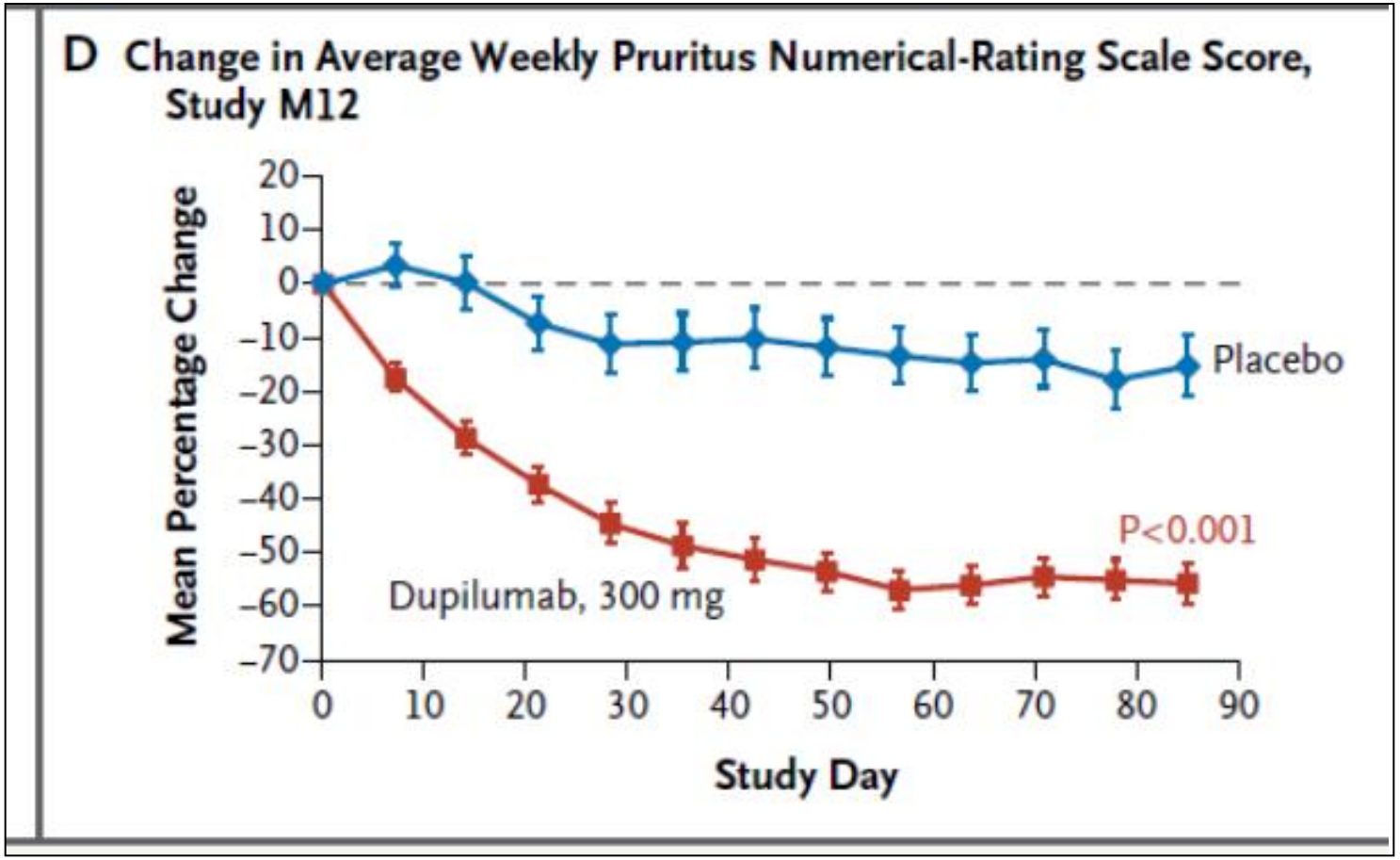
[1]Beck LA, Thaçi D, Hamilton JD, et al. Dupilumab treatment in adults with moderate-to-severe atopic dermatitis. N Engl J Med. 2014;371:130-9

Results-Key Efficacy Endpoints M12



[1]Beck LA, Thaçi D, Hamilton JD, et al. Dupilumab treatment in adults with moderate-to-severe atopic dermatitis. N Engl J Med. 2014;371:130-9

Results-Key Efficacy Endpoints M12



[1]Beck LA, Thaçi D, Hamilton JD, et al. Dupilumab treatment in adults with moderate-to-severe atopic dermatitis. N Engl J Med. 2014;371:130-9

Reported Results-Safety

- Adverse events, lab abnormalities, changes in EKGs and vital signs were reported to be similar between placebo and dupilumab groups
- Most common AEs reported more frequently by dupilumab-treated subjects
  - nasopharyngitis, headache, injection site reactions

[1]Beck LA, Thaçi D, Hamilton JD, et al. Dupilumab treatment in adults with moderate-to-severe atopic dermatitis. N Engl J Med. 2014;371:130-9

Reported Results-Safety

- Serious AEs (SAEs) reported in the 12 wk monotherapy study: placebo > dupilumab
- SAEs reported in all studies
  - 13 SAEs in 9/80 subjects on placebo
  - 2 SAEs in 2/127 subjects on dupilumab
- Imbalance in SAEs due to skin infections and AD flares

[1]Beck LA, Thaçi D, Hamilton JD, et al. Dupilumab treatment in adults with moderate-to-severe atopic dermatitis. N Engl J Med. 2014;371:130-9

Questions?

Ethical Considerations in the Development of Products for use in Pediatric Patients with Atopic Dermatitis

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Michelle.Roth-Cline@fda.hhs.gov

Introduction

- We have evolved from a view that we must protect children from research to a view that we must protect children through research.

- Seeking to avoid "N of 1" (single-patient) trials resulting from insufficient knowledge of dosing, safety and efficacy of drugs in children

- Thus, protecting children requires data to support the safe and effective use of drugs and biological products in infants, children and adolescents.

Basic Ethical Framework in Pediatrics

1. Children should only be enrolled if scientific and/or public health objective(s) cannot be met through enrolling subjects who can consent personally
2. Absent a prospect of direct therapeutic benefit, the risks to which children are exposed must be "low"
3. Children should not be placed at a disadvantage by being enrolled in a clinical trial
4. Vulnerable populations unable to consent (including children) should have a proxy to consent for them

Additional Safeguards for Children

21 CFR 50 and 45 CFR 46 Subpart D

2,3: Appropriate Balance of Risk and Benefit

- Research involving children either
  - must be restricted to "minimal" risk or a "minor increase over minimal" risk absent a potential for direct benefit to the enrolled child, or
    - *21 CFR 50.51/21 CFR 50.53*
  - must present risks that are justified by anticipated direct benefits to the child; the balance of which is at least as favorable as any available alternatives.
    - *21 CFR 50.52*

Linking Science and Ethics

- Ethical challenge is to establish sufficient scientific data using either preclinical animal models or adult human clinical trials to conclude that:

  1) *"Low Risk" Pathway*: Absent sufficient prospect of direct benefit, administration of investigational product to children presents an acceptably "low" risk, or…

     - 21 CFR 50.51/50.53 (cf. ICH E-6 §4.8.14)

  2) *"Higher Risk" Pathway*: Administration of investigational product to children presents a sufficient prospect of direct benefit to justify "higher" risks.

     - 21 CFR 50.52

Higher Risk Pathway
21 CFR 50.52

- Clinical investigations that present the prospect of direct benefit may be approvable if:
  - The risk is justified by the anticipated benefit to the subjects;
  - The relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches
  - Assent and permission obtained

Modeled on Clinical Decision-making

- Given what is known about the potential risks and benefits of the investigational product, would a reasonable clinician be willing to administer it to patients in the study population, after considering the nature and severity of the disease in the study population and the other therapeutic options available to those patients?
- (The willingness of a clinician to give a product does not *per se* indicate that the product works)

Timing of Pediatric Studies

- Product is being developed for both a pediatric and adult indication (goal: concurrent licensure).
  - Sequential Development (linear or staggered)
    - The results (efficacy and/or safety) of adult studies are necessary to inform pediatric development.
  - Parallel Development
    - Pediatric and adult development may proceed together, based on data supporting the initiation of pediatric clinical trials.
- Pediatric studies should be initiated as soon as sufficient information is available to meet the ethical and regulatory requirements (21 CFR 50.52)

Two Choices

A child in the study population may be treated with a particular new therapeutic agent for AD, because the balance of risks and benefits of that agent appears to be at least as favorable to that child as other systemic agents.

OR

We should obtain more information regarding the risks and benefits of the new agent in adults, because we do not yet have sufficient information to conclude that the balance of risks and benefits of the new agent may be considered similar to other systemic agents.

Considerations: Risk Justification

- Seriousness of the disease and impact on health and quality of life
- Probability and magnitude of harm and potential benefits from the drug vs. alternatives
- Degree of tolerable uncertainty about the probability of harm given the known risks of the disease (and other agents)

Broader Context

- When the drug is likely to be marketed for any indication
- How patients and their clinicians would answer benefit/risk questions
- Other indications for which the drug is under development

Population With Medical Need

- Systemic agents recommended in the following patients:
  - Topical regimens and/or phototherapy do not adequately control signs and symptoms
  - Patient's skin disease has significant negative physical, emotional, or social impact

-2014 American Academy of Dermatology Guidelines of Care

Currently Used Therapies (Off-Label)

- Cyclosporine
- Azathioprine
- Methotrexate
- Mycophenolate mofetil
- Systemic steroids (bridge to other agents)

-2014 American Academy of Dermatology Guidelines of Care

Lessons from Past Products

- If a product is marketed in adults and represents a meaningful therapeutic benefit, at least some patients and clinicians may be willing to accept the risk and use the product in children
- If off-label use becomes common, pediatric RCTs (while ethical) may be difficult or impossible if patients refuse to enroll or clinicians refuse to participate
- Products become standard of care absent information about the risks and benefits in children

Thank you!

Questions?

Questions for the Committee

Please discuss the timing and inclusion of pediatric subjects in trials of systemic products (drugs and biologics) for the treatment of atopic dermatitis that is inadequately responsive to topical therapy, in the context of an ongoing adult development program. Specifically, please address the following:

1. **DISCUSSION:** Is there an unmet medical need for systemic products (drugs and biologics) approved for treatment of children with atopic dermatitis that is inadequately responsive to topical therapy?

Questions for the Committee

2. **DISCUSSION:** How much evidence of treatment effect and safety should be obtained in adults prior to studying the use of a novel agent in the treatment of children with atopic dermatitis that is inadequately responsive to topical therapy:
   - preliminary efficacy and safety data (early-phase trial/s)?
   - determinative efficacy and safety data (phase 3 trials)?
   - post-marketing adverse event data?

Questions for the Committee

3. **DISCUSSION:** How much uncertainty about the potential risks and benefits of novel agents is tolerable when initiating a pediatric trial, given the nature of the disease (severity, co-morbidities, impact on quality of life) and the risk-benefit calculus of available alternative treatments (e.g., systemic corticosteroids, cyclosporine, azathioprine, methotrexate, mycophenolate mofetil)? Address whether enrollment of pediatric subjects would be acceptable prior to the resolution of questions regarding potential risk for low-frequency or long-latency adverse events.

Questions for the Committee

4. **DISCUSSION:** Describe the appropriate pediatric population in whom to study systemic treatments such that the risks and potential benefits of the investigational agent could be compared to the population who receive alternative treatments (e.g., systemic corticosteroids, cyclosporine, azathioprine, methotrexate, mycophenolate mofetil). Address disease severity, prior treatment, age, and any other relevant factors.

Questions for the Committee

5. **DISCUSSION**: Address the importance of having sufficient data to label the product for use in some or all pediatric subpopulations at the time of an adult approval in order to avoid the risks of "off-label" use in children.

6. **DISCUSSION:** Describe the age range that should be studied, and address whether older pediatric subpopulations should be studied prior to or concurrently with younger pediatric subpopulations (e.g., 12-<17 years, 6-<12 years, 2-<6 years, 6 months -<2 years)?